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# The Efficacy and Safety of Vertebral Augmentation: A Second ASBMR Task Force Report

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## ABSTRACT

Vertebral augmentation is among the current standards of care to reduce pain in patients with vertebral fractures (VF), yet a lack of consensus regarding efficacy and safety of percutaneous vertebroplasty and kyphoplasty raises questions on what basis clinicians should choose one therapy over another. Given the lack of consensus in the field, the American Society for Bone and Mineral Research (ASBMR) leadership charged this Task Force to address key questions on the efficacy and safety of vertebral augmentation and other nonpharmacological approaches for the treatment of pain after VF. This report details the findings and recommendations of this Task Force. For patients with acutely painful VF, percutaneous vertebroplasty provides no demonstrable clinically significant benefit over placebo. Results did not differ according to duration of pain. There is also insufficient evidence to support kyphoplasty over nonsurgical management, percutaneous vertebroplasty, vertebral body stenting, or KIVA®. There is limited evidence to determine the risk of incident VF or serious adverse effects (AE) related to either percutaneous vertebroplasty or kyphoplasty. No recommendation can be made about harms, but they cannot be excluded. For patients with painful VF, it is unclear whether spinal bracing improves physical function, disability, or quality of life. Exercise may improve mobility and may reduce pain and fear of falling but does not reduce falls or fractures in individuals with VF. General and intervention-specific research recommendations stress the need to reduce study bias and address methodological flaws in study design and data collection. This includes the need for larger sample sizes, inclusion of a placebo control, more data on serious AE, and more research on nonpharmacologic interventions. Routine use of vertebral augmentation is not supported by current evidence. When it is offered, patients should be fully informed about the evidence. Anti-osteoporotic medications must be initiated as soon as practicable, continued, or changed. © 2019 American Society for Bone and Mineral Research.

**KEY WORDS:** VERTEBRAL FRACTURE; VERTEBRAL AUGMENTATION; VERTEBROPLASTY; KYPHOPLASTY; OSTEOPOROSIS

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Executive Summary

Introduction

Vertebral compression fractures are highly prevalent in patients with osteoporosis, and approximately 750,000 new fractures occur each year in the United States alone.<sup>(1,2)</sup> Acute and chronic back pain occur in approximately one-third of patients with vertebral fractures, resulting in disability and impaired quality of life. Vertebral augmentation (percutaneous vertebroplasty or balloon kyphoplasty) to reduce pain in patients with symptomatic vertebral fractures was introduced into practice before high-quality evidence establishing its efficacy and safety and remains in some settings part of standard routine care. Balloon kyphoplasty is currently more expensive and is performed almost three times more commonly than percutaneous vertebroplasty in the United States.<sup>(3)</sup> Two placebo-controlled trials of percutaneous vertebroplasty published in 2011 questioned the value of this procedure, and an additional three trials, all in participants with acute symptoms (for up to 9 weeks), have now confirmed the findings of these earlier trials. No placebo-controlled trials of balloon kyphoplasty have been performed and evidence of the value of this procedure is reliant on low-quality evidence from trials that have compared kyphoplasty with usual care or head-to-head comparisons with vertebroplasty. In addition, there have been few trials of other nonpharmacological approaches to reduce pain in patients with vertebral fractures.

Task Force process

The American Society for Bone and Mineral Research (ASBMR) leadership charged this Task Force to address key questions on the efficacy and safety of vertebral augmentation and other nonpharmacological approaches for the treatment of vertebral fracture (Table 1). This report details the findings and

recommendations of this Task Force. The work of this report builds upon that of a related ASBMR Task Force Report published in 2017 that addressed pain, quality of life, and safety outcomes associated with kyphoplasty for vertebral fractures, which is summarized in detail in Section 2, Balloon Kyphoplasty, below.<sup>(4)</sup>

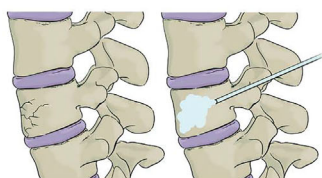
The efficacy and safety of vertebral augmentation, either percutaneous vertebroplasty or balloon kyphoplasty (Fig. 1), and other nonpharmacologic treatments for painful vertebral fractures, such as spinal bracing (Fig. 2), were assessed by a systematic review of the existing literature and meta-analyses (when appropriate) of outcomes including mean overall pain, disability, disease-specific and overall health-related quality of life, patient-reported treatment success, new symptomatic vertebral fractures, and number of other serious adverse events (AE) versus a comparator group, including placebo or a sham procedure. Although new symptomatic vertebral fractures after vertebral augmentation are considered a harm, they could also represent a relapse of the primary event related to osteoporosis. We included randomized controlled trials (RCTs) and quasi-randomized trials that enrolled adults aged >40 years with acute nontraumatic vertebral fractures and directly compared percutaneous vertebroplasty or balloon kyphoplasty versus any treatment comparator group (eg, placebo, sham procedure, standard medical care, exercise, manual therapy, braces, electrotherapy, electro-acupuncture, percutaneous vertebroplasty, balloon kyphoplasty, pharmacologic treatment, or other nonpharmacologic intervention). Risk of bias was assessed according to the Cochrane risk of bias tool. Important considerations in interpreting trial data are timing of benefits and harms of the interventions. Benefits such as improvements in pain could be anticipated to occur early after an intervention, while harms such as incident vertebral fractures, could be anticipated to occur over both the shorter and longer term.

Table 1. ASBMR Task Force Charges and Key Questions

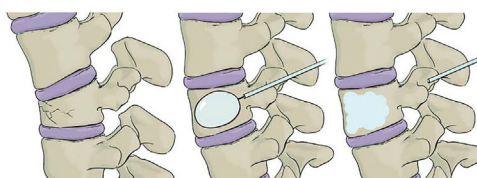
Task Force charge	Key questions addressed
Conduct systematic literature review, and meta-analysis if appropriate, to address what is currently known and not known about the safety and efficacy of vertebral augmentation, including reviewing the evidence to assess if vertebral fracture risk is increased after vertebral augmentation.	1. What is the efficacy and relative effectiveness of percutaneous vertebroplasty in improving pain, physical function, and quality of life? 2. What is the efficacy and relative effectiveness of balloon kyphoplasty in improving pain, physical function, and quality of life? 3. What are the harms of percutaneous vertebroplasty, including possible risk of new vertebral fractures? 4. What are the harms of balloon kyphoplasty, including possible risk of new vertebral fractures?
Consider the safety and efficacy of other nonpharmacologic treatments for individuals with vertebral fracture, such as braces and lumbar support corsets, transcutaneous electrical nerve stimulation, and exercise programs, and compare them to vertebral augmentation.	5. What is the safety and efficacy of other nonpharmacologic treatments, such as spinal bracing, after vertebral fracture? 6. What is the safety and efficacy of exercise interventions after vertebral fracture?
Identify the key questions and knowledge gaps to offer a research agenda that will determine the safety and efficacy of vertebral augmentation, as well as other nonpharmacologic approaches for the management of osteoporotic vertebral fractures.	7. What research is needed to fill knowledge gaps to improve patient outcomes in managing osteoporotic vertebral fractures, either through vertebral augmentation or other nonpharmacologic approaches?

## Vertebral Augmentation

Percutaneous Vertebroplasty



Balloon Kyphoplasty



**Fig. 1.** Percutaneous vertebroplasty and balloon kyphoplasty.

For the nonsurgical interventions, we included RCTs and quasi-randomized trials of bracing or exercise interventions with similar enrollment criteria as noted above and compared the treatment groups to all comparators, including placebo. For each article identified, two reviewers independently extracted data on study design, participant characteristics, intervention characteristics, outcomes, and AE. Risk of bias was rated as high, moderate, or low by two independent examiners, according to the Cochrane risk of bias tool.

### Overview of Task Force recommendations and findings

All Task Force members reviewed the final Task Force recommendations and, based on responses to questionnaires, the majority agreed on each recommendation for each of the three interventions. Task Force recommendations and findings are summarized in Table 2. Detailed methods of the systematic reviews and meta-analyses may be found in the supplemental pages of the ASBMR Task Force report. Task Force recommendations for future research are summarized in Table 3. Guidance for the clinical management of patients with acute

vertebral fracture, based on the recommendations and findings of the Task Force, is also offered, despite not being a Task Force charge, nor a key question, and this is also summarized in Table 3.

### Comparator procedures and blinding

In the context of vertebral augmentation, placebo is exactly the same as the actual treatment, except for the active ingredient, ie, injection of bone cement into the vertebra. A sham procedure means that local anesthetic was administered to the skin and the procedure was simulated. It is important for assessing true efficacy that patients and outcome assessment be blinded to reduce the risk of performance and detection bias. An assessment of the success of blinding should also be undertaken. Trials comparing augmentation to controls, such as usual care, are at high risk of bias because of the risk of performance and detection bias and overestimate the benefits of augmentation procedures. This is essential for trials that evaluate conditions with a favorable natural history and/or that measure patient-reported outcomes, as this can control for the effect of contextual factors (placebo, regression to the mean, favorable natural history, eg, diminishing pain after a vertebral fracture) to determine an intervention's true effect (or true efficacy). Results of studies for painful osteoporotic vertebral fractures that do not include a placebo control and do not blind participants and/or outcome assessment should be interpreted with caution because they overestimate the treatment effect (usually by around 25% to 30%). When evidence was only available from trials that did not include a placebo control, it was graded as low, with the corresponding strength of recommendation being weak.

### Conclusion

The recommendations by this Task Force are designed to help provide a foundation for advancing the research and clinical care of patients with painful acute vertebral fractures. The current evidence does not support the use of vertebroplasty and this is likely to apply to other augmentation procedures like kyphoplasty, although high-quality evidence from placebo-controlled trials are absent. In making quality, informed patient care decisions, clinicians will need to balance the limited findings on the safety and efficacy of other non-pharmacologic interventions with good clinical judgment. Fully disclosing the evidence to patients will ensure that they can make the best evidence-informed decisions about their care.



**Fig. 2.** SpinoMed back orthosis. (Reproduced with permission from Pfeifer M, Begerow B, Minne HW. Effects of a new spinal orthosis on posture, trunk strength, and quality of life in women with postmenopausal osteoporosis: a randomized trial. *Am J Phys Med Rehabil*. 2004;83:177–86. DOI: 10.1097/01.PHM.0000113403.16617.93.)

**Table 2.** Summary of ASBMR Task Force Recommendations and Findings of Key Questions for Patients With Acutely Painful Vertebral Fractures

Key question addressed	Task Force recommendation/finding	Quality of evidence	Strength of findings	Strength of recommendation
1. Efficacy of percutaneous vertebroplasty on outcomes of pain, physical function, and quality of life	Percutaneous vertebroplasty provides no demonstrable clinically significant benefit over placebo or sham procedure. Results did not differ according to duration of pain.	High to moderate	High—5 randomized trials that compared vertebroplasty with placebo ( $n = 535$ ). Follow-up period 2 years.	High to moderate
2. Efficacy of balloon kyphoplasty on outcomes of pain, physical function, and quality of life	Balloon kyphoplasty provides a small clinical benefit over nonsurgical management, percutaneous vertebroplasty, vertebral body stenting, or KIVA. There is also insufficient evidence versus placebo for KIVA.	Low	Low—1 randomized trial versus nonsurgical management. No placebo ( $n = 300$ ). Follow-up period 2 years.	Weak
3. Harms of percutaneous vertebroplasty, including possible risk of new vertebral fractures	It is uncertain whether percutaneous vertebroplasty increases risk of incident or radiographic vertebral fractures or related serious AEs.	Moderate	Moderate—8 randomized trials (placebo control in 4 trials and usual care in 4 trials) ( $n = 804$ ). Low number of events ( $n = 203$ fractures; 57 SAEs). Follow up period 1–2 years.	Moderate
4. Harms of balloon kyphoplasty, including possible risk of new vertebral fractures	It is uncertain whether kyphoplasty increases risk of incident or radiographic vertebral fractures or serious AE related to kyphoplasty.	Low	Low—1 randomized trial versus nonsurgical management ( $n = 223$ ) and case reports. Low number of events ( $n = 101$ fractures; 157 SAEs). Follow-up period 2 years.	Weak
5. Efficacy and harms of spinal bracing after vertebral fracture	It is uncertain whether spinal bracing may improve physical function, disability, or quality of life.	Low	Low—4 randomized trials comparing orthoses ( $n = 281$ ). High risk of bias due to absent blinding of subjects and investigators. Low numbers of fractures and AEs. Follow-up period 3 weeks to 6 months.	Weak
6. Efficacy and harms of exercise interventions after vertebral fracture	Exercise may improve mobility and reduce pain and fear of falling. It is uncertain whether exercise improves balance, back extensor strength, reduces falls, and was safe.	Moderate to low	Low—9 randomized trials comparing exercise with usual care ( $n = 749$ ). Low to high risk of bias due to absent blinding of subjects and investigators. Low numbers of events ( $n = 15$ fractures; 5 SAEs). Follow-up period 4 weeks to 2 years.	Weak

## The Efficacy and Safety of Vertebral Augmentation: Task Force Recommendations and Findings

Vertebral compression fractures are highly prevalent in patients with osteoporosis, and approximately 750,000 new fractures occur each year in the United States alone.<sup>(1,2)</sup> Acute and chronic back pain, occurring in approximately one-third of patients with vertebral fractures, result in disability and impaired quality of life. Pain from vertebral fractures may be managed through both vertebral augmentation and nonpharmacological approaches. Considering the increasing number of elderly individuals conferred by population aging, vertebral fractures are anticipated to increase and, thus, current treatment strategies deserve attention.

Vertebral augmentation is among the current standards of care to reduce pain in patients with vertebral fractures, yet a

lack of consensus regarding efficacy and safety of percutaneous vertebroplasty and kyphoplasty raises questions, on what basis clinicians should choose one therapy over another. Of approximately 300,000 inpatient vertebral augmentation procedures performed in the United States between 2005 and 2010, 73% were kyphoplasty and 27% were percutaneous vertebroplasty.<sup>(3)</sup> As patient outcomes for these pain management strategies and nonpharmacological approaches have not been compared to establish the relative benefits and harms of these treatments, clinicians are left with inadequate information to make decisions regarding optimal patient care.

Given the lack of consensus in the field, ASBMR leadership charged this Task Force to address key questions on the efficacy and safety of vertebral augmentation and other nonpharmacological approaches for the treatment of pain

**Table 3.** Summary of ASBMR Task Force Recommendations for Future Research and Guidance on Clinical Management

**Future research needed to improve patient outcomes in managing osteoporotic vertebral fractures, either through vertebral augmentation or other nonpharmacologic approaches** General research needs

Percutaneous vertebroplasty and kyphoplasty

Bracing and exercise interventions

**Guidance for clinical management of patients with acute vertebral fracture**

- Future trials should identify other novel and potentially useful interventions for pain after vertebral fracture.
- trials should ensure adequate sample sizes to answer the research question.
- trials should have inclusion criteria that allow generalizable conclusions to be drawn for the population that experiences these acute vertebral fractures outside research settings.
- Include cost-effectiveness outcomes.
- anti-osteoporosis therapy as part of interventions.
- registries may be helpful for widespread systematic data collection for safety after vertebral augmentation.
- More trials are needed exploring exercise or rehabilitation interventions in the acute/subacute stage after vertebral fracture.
- Research on de-implementation of vertebroplasty to reduce any potential harms of the procedure should be considered.
- No further trials of vertebroplasty should be performed, unless they are large and adequately powered to alter the conclusions of the current body of evidence that concludes that the procedure is no more effective than placebo and the benefits are unlikely to outweigh any harms of the procedure.
- Any further trials of kyphoplasty should have a placebo control group.
- More data are needed on potential harms, including new and adjacent vertebral fractures, and cement leakage.
- Potential participants in any further trials of these procedures should be fully informed about the current body of evidence.
- Ethics committees should also be fully informed about the current body of evidence to inform their decision about the ethics of any further trials.
- More research is needed in nonsurgical interventions in general, including more clearly defined participant selection criteria and study protocols (including the frequency, intensity, time, and type of intervention used).
- More rigorous trial design (eg, placebo procedure, blinding of outcome assessors, use of validated outcome measures, patient selection generalizable to clinical setting) is needed to reduce bias potential and improve adherence and attrition.
- The optimal management of vertebral fracture is uncertain. Routine use of vertebral augmentation is not supported by current evidence. When it is offered, patients should be fully informed about the evidence.
- Anti-osteoporotic medications must be initiated as soon as practicable, or continued, in patients with a recent vertebral fracture. A change in treatment may also need to be considered if the vertebral fracture occurred after 12 months from initiation of anti-osteoporotic treatment.
- Use of bracing in reducing pain immediately after vertebral fracture is not supported by current evidence.
- Exercise may improve mobility and may reduce pain and fear of falling. However, the use of exercise to improve other outcomes is not supported by current evidence.

from acute vertebral fracture. It is important to note that studies on pathological vertebral fractures were excluded. The Task Force findings and recommendations are summarized below.

**Key Questions 1 and 2: What is the efficacy and relative effectiveness of vertebral augmentation therapy in improving pain, posture, physical function, and quality of life?**

**Recommendation/finding:** For patients with acutely painful osteoporotic vertebral fracture, percutaneous vertebroplasty provides no demonstrable clinically important benefits compared with placebo or sham procedure. There is insufficient evidence to support kyphoplasty over nonsurgical management, percutaneous vertebroplasty, vertebral body stenting, or KIVA.



**Quality of evidence:** Moderate to high for percutaneous vertebroplasty; low for kyphoplasty

**Strength of recommendation/finding:** High for percutaneous vertebroplasty; weak for kyphoplasty

## Evidence in support of recommendation/finding

### 1. Percutaneous vertebroplasty

Percutaneous vertebroplasty is a minimally invasive, fluoroscopy-guided therapy used to relieve pain from an acute vertebral fracture. It usually involves the percutaneous injection of a bone cement, polymethylmethacrylate (PMMA), into the vertebral body via the pedicle of the vertebra (Fig. 1). The aim of this procedure is to reduce pain by stabilizing the vertebral fracture.

This section is a summary and update of a recent systematic review on percutaneous vertebroplasty for osteoporotic vertebral compression fracture.<sup>(5)</sup> Outcomes for percutaneous vertebroplasty trials were compared with either placebo or standard medical care.

#### a) Percutaneous vertebroplasty versus placebo

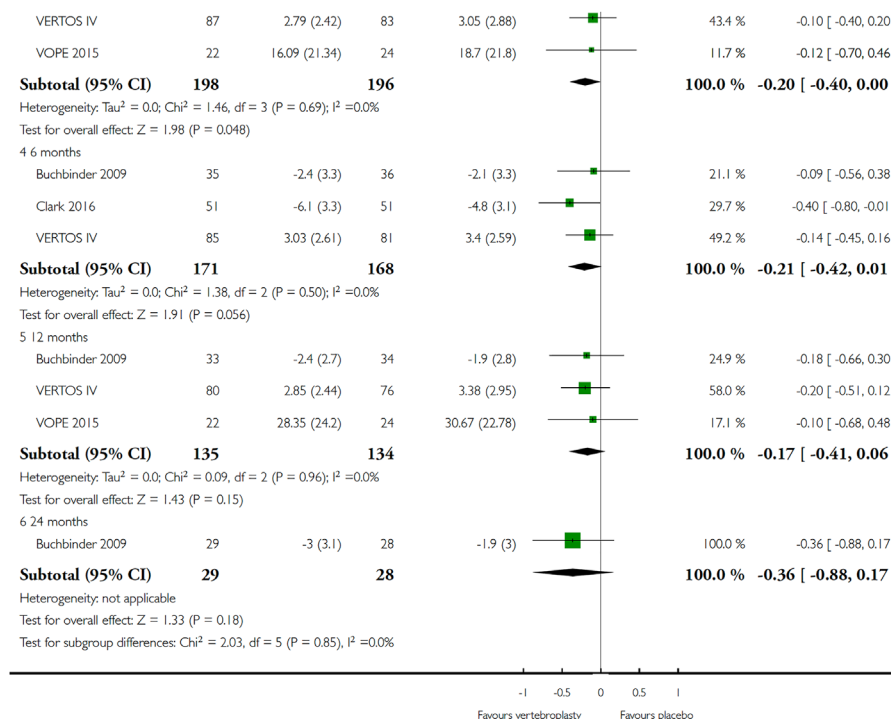
The updated Cochrane review included five randomized trials that compared vertebroplasty with placebo.<sup>(6–12)</sup> Three trials only included participants with pain for 9 weeks or less. Three trials were considered to be at low risk of bias, whereas two were possibly at risk of performance and detection bias. There was high-quality evidence that percutaneous vertebroplasty conferred no clinically important benefits with respect to pain, disability, or disease-specific quality of life, and moderate quality

evidence of no important benefits for overall quality of life and treatment success. Numerical data are presented for the 1-month outcomes where available.

Efficacy findings are as follows:

**Pain:** At 1 month, there was a small and clinically unimportant difference in pain favoring the vertebroplasty group (mean difference [MD]  $-0.62$  [95% CI  $-10.1$  to  $-0.23$ ] on a scale of 0 to 10, no statistical heterogeneity) (five trials, 535 participants). Mean pain was five points in the placebo group and 0.6 points better (0.2 to 1 better) in the vertebroplasty group. There were also no between-group differences in the proportion of participants who improved from baseline by 2.5 units or more or by 30% or more at 1 month based upon pooled data from 3 trials (89/166 in the percutaneous vertebroplasty group versus 56/160 in the placebo group, risk ratio [RR] 1.53 [95% CI 0.99 to 2.36]), but there was substantial statistical heterogeneity ( $I^2 = 61\%$ ). Based upon data from up to five trials (539 participants), no between-group differences in mean pain or proportion who improved from baseline according to the above parameters were observed at 1 to 2 weeks or other endpoints up to 2 years (Fig. 3).

**Disability:** Based upon four trials (472 participants), there was a small and clinically unimportant difference in disability at 1 month favoring vertebroplasty (MD  $-1.50$ , 95% CI  $-2.61$  to  $-0.38$ ), measured with the Roland Morris Disability Questionnaire (RMDQ) (0–23 scale, higher scores indicated greater disability). Mean disability at 1 month (187 participants) in the placebo group was 14.2 points, and 1.5 points better (0.4 better to 2.6 better) in the vertebroplasty group, and there was no



**Fig. 3.** Forest plot of the efficacy outcome: vertebroplasty versus placebo (sham), pain (0 to 10 point scale)<sup>5</sup>.

statistical heterogeneity. There were no between-group differences in disability at any of the other time points based upon up to four trials (475 participants).

**Quality of life:** Based upon three trials (351 participants), there was no between-group difference in vertebral fracture and/or osteoporosis-specific health-related quality of life as measured by the QUALEFFO (0–100 scale, higher scores indicating worse quality of life) at 1 month. Mean QUALEFFO was 62 points in the placebo group and 2.3 points better in the vertebroplasty group (1.4 points worse to 6.7 points better) (MD –2.33, 95% CI –6.06 to 1.41),  $I^2 = 36\%$  indicating unimportant heterogeneity). There were also no between-group differences at other time points based upon up to three trials and 352 participants. Similarly, there were no between-group differences in overall quality of life at any time point up to 2 years (up to three trials and 285 participants).

**Treatment success:** One trial measured participant global assessment of treatment success defined as “moderately better” or “a great deal better” on a 7-point ordinal scale and observed no between-group differences up to 24 months.<sup>(7,8)</sup> Specifically, based upon 78 participants, at 1 month 225 per 1000 in the sham group and 315 per 1000 in the percutaneous vertebroplasty group perceived treatment success (relative risk 1.40 [95% CI 0.67 to 2.95]).

#### **b) Percutaneous vertebroplasty versus standard medical (nonsurgical) care**

There were eight trials that compared percutaneous vertebroplasty with standard medical care (1136 randomized participants),<sup>(13–20)</sup> and they were considered sufficiently clinically homogenous to allow data pooling. Trial participants had similar levels of baseline pain and disability, and sex distribution was also similar, although one trial included younger participants,<sup>(14)</sup> and the duration of symptoms across trials varied from 1 week<sup>(17)</sup> to 6 months.<sup>(15)</sup>

Efficacy findings are as follows:

**Pain:** Based upon data from up to six trials, the analysis favored the percutaneous vertebroplasty group, who had greater improvement in mean pain compared with the usual care group at 1 month (three trials, 384 participants, mean difference –3.30 (95% CI –5.36 to –1.22). Similar results were observed at 1 to 2 weeks and at other time points up to 1 year, but there was considerable statistical heterogeneity across all pooled pain analyses with the  $I^2$  varying between 94% and 96%. At 24 months, there was no between-group difference in mean pain based upon one trial.

**Disability:** Based upon data from up to five trials (494 participants), improvement in disability also favored the percutaneous vertebroplasty group at all time points (MD at 1 month –6.38 (95% CI –12.60 to –0.17), three trials, 378 participants,  $I^2 = 97\%$ ). Considerable statistical heterogeneity was also present for all other analyses ( $I^2$  ranging from 97% to 98%).

**Quality of life:** There was no significant between-group differences with respect to vertebral fracture or osteoporosis-specific quality of life at any time point measured by the

QUALEFFO up to 1 year, based upon data from up to 4 trials and 448 participants (1 month: two trials, 289 participants, mean difference –10.18 (95% CI –21.49 to 1.13),  $I^2 = 95\%$ ). Considerable statistical heterogeneity was also present for all analyses ( $I^2$  varying between 83% and 95%). Overall quality of life measured by the EQ-5D marginally favored the percutaneous vertebroplasty group at 1 month (one trial, 183 participants, mean difference 0.09 [95% CI 0.01 to 0.16]). It also marginally favored vertebroplasty at 1 to 2 weeks, 3 and 6 months, but not 1 year. Statistical heterogeneity was unimportant for the pooled analyses ( $I^2$  ranged from 0% to 22%).

**Treatment success:** This outcome was not reported in any of the trials comparing percutaneous vertebroplasty with standard care.

#### **c) Subgroup analysis**

The updated Cochrane review explored the effects of vertebroplasty according to symptom duration (“acute” versus “subacute” pain) in a subgroup analysis for outcomes of pain and disability at 1 to 2 weeks and 1 month. Data for “acute” fractures included trials that only included participants with pain less than 6 weeks,<sup>(8)</sup> 8 weeks or less,<sup>(10)</sup> or 9 weeks or less,<sup>(9)</sup> as well as the participants with symptom duration of 6 weeks or less in two other trials.<sup>(6,7)</sup> No important differences in outcomes were found. Excluding data for the two trials, a longer duration of “acute” fractures<sup>(9,10)</sup> did not alter the results.

#### **d) Sensitivity analysis**

Combining data for the five placebo-controlled trials with the eight open trials that compared vertebroplasty with usual care altered the results in favor of vertebroplasty for all end points assessed in the sensitivity analysis (pain and disability at 1 to 2 weeks, 1 and 3 months). There was considerable heterogeneity, largely due to heterogeneity of results in the open trials.

#### **Summary of percutaneous vertebroplasty**

Based upon high- to moderate-quality evidence from five randomized placebo-controlled trials, percutaneous vertebroplasty provides no demonstrable clinically important benefits compared with placebo for people with acutely painful osteoporotic vertebral fractures. Subgroup analyses in the updated Cochrane review indicated that the results did not differ according to duration of pain, whereas the sensitivity analyses indicate that open trials that compared percutaneous vertebroplasty with standard medical care are likely to have overestimated any benefit of percutaneous vertebroplasty.

### **2. Balloon kyphoplasty**

Balloon kyphoplasty is similar to percutaneous vertebroplasty with the difference being that a balloon or bone tamp is introduced via the vertebral pedicle into the vertebral body, where it is inflated to create a cavity into which a percutaneous injection of a bone cement, PMMA, is made (Fig. 1). This procedure also aims to restore vertebral height and lessen spinal deformity.

This section is an update on findings pertaining to balloon kyphoplasty. A literature search was performed, and risk of bias was assessed. Database searches yielded 2460 unique references. We excluded 2406 during title and abstract review and 40 during full-text review, leaving 14 reports of 10 unique studies



that met eligibility criteria and were included for analysis.<sup>(21–34)</sup> Studies of vertebral fractures resulting from malignancy were excluded. Among the 10 unique eligible studies, eight were rated as having high risk of bias,<sup>(21,23–26,29–34)</sup> and two were rated as uncertain.<sup>(22,27,28)</sup> The most common sources of bias were lack of blinding, incomplete reporting of outcomes, and inadequate or uncertain concealment of treatment allocation. However, it would not have been possible to mask participants between kyphoplasty and non-balloon kyphoplasty and surgical management without use of a sham procedure, or to mask assessors of radiographic outcomes to the vertebral cement in the kyphoplasty group. Further details regarding this review can be found in the full report.<sup>(4)</sup>

The included studies compared kyphoplasty with nonsurgical management, percutaneous vertebroplasty, another vertebral augmentation device (KIVA®), and vertebral body stenting.

### a) Balloon kyphoplasty versus nonsurgical management

Five RCTs (two unique trials) met eligibility criteria. The FREE trial ( $n = 300$ )<sup>(23,24,30,33)</sup> used computer-generated permuted block randomization, after which participants and study staff were unblinded. Follow-up was 24 months. Yi and colleagues ( $n = 200$ ) stated participants were randomized, and treatment assignment was blindly chosen by a single surgeon.<sup>(34)</sup> Outcome assessors were blinded to treatment assignment, and follow-up was 48 months. In the FREE trial, mean age was 72.2 years, and 77% of participants were female.<sup>(23,24,30,33)</sup> Qualifying vertebral fractures were most commonly located at the thoracolumbar junction and had occurred a mean of 6 weeks before randomization. Vertebral fractures were attributed to osteoporosis (40% of participants had a spine T-score  $< -2.5$ ).<sup>(23,24,30)</sup> At baseline, participants reported severe back pain (mean VAS 6.8 out of 10), substantial back-related disability (mean RMDQ score 17.5), and poor health-related quality of life (mean Short Form-36 Physical Component Summary Scale [SF-36 PCS] score 25.7 and mean EQ-5D score 0.18). In Yi and colleagues,<sup>(34)</sup> mean age was 61.3 years, and 62% were female. Qualifying vertebral fractures were described as symptomatic. Prevalence of osteoporosis was not specified, and no data were reported on number of fractures per participant, fracture location, use of bone active medications, or participant baseline pain, disability, or quality of life.

Efficacy findings are as follows:

**Pain:** Kyphoplasty was associated with significantly more reduction in pain than nonsurgical management at all time points, though the relative difference between groups in improvement in VAS appeared to diminish over time: mean difference at 1 month =  $-1.82$  [ $-2.37, -1.27$ ;  $n = 264$ ]; at 3 months =  $-1.45$  [ $-2.01, -0.89$ ;  $n = 246$ ]; at 6 months =  $-1.48$  [ $-2.05, -0.91$ ;  $n = 241$ ]; at 12 months =  $-0.84$  [ $-1.42, -0.26$ ;  $n = 226$ ]; and at 24 months =  $-0.69$  [ $-1.27, -0.11$ ;  $n = 200$ ].

**Disability:** Kyphoplasty was associated with significantly more reduction in the RMDQ scale than nonsurgical management at 30 days ( $-4.20$  [ $-5.54, -2.86$ ;  $n = 255$ ]), 3 months ( $-3.69$  [ $-5.10, -2.28$ ;  $n = 225$ ]), 6 months ( $-3.05$  [ $-4.50, -1.60$ ;  $n = 230$ ]), and 12 months ( $-2.90$  [ $-4.37, -1.43$ ;  $n = 204$ ]) but not at 24 months ( $-1.43$  [ $-2.91, 0.05$ ;  $n = 193$ ]). The relative reduction in disability after kyphoplasty compared with nonsurgical management also appeared to diminish with time.

**Quality of life:** Kyphoplasty was associated with significantly more improvement in the SF-36 score than nonsurgical management at 1 month ( $5.40$  [ $3.14, 7.66$ ;  $n = 261$ ]), 3 months ( $4.00$  [ $1.67, 6.33$ ;  $n = 241$ ]), and 6 months ( $3.30$  [ $1.00, 5.60$ ;  $n = 237$ ]) but not at 12 months ( $1.60$  [ $-0.73, 3.93$ ;  $n = 225$ ]) or 24 months ( $1.50$  [ $-0.83, 3.83$ ;  $n = 186$ ]). By comparison, kyphoplasty was associated with significantly more improvement than nonsurgical management on the EQ-5D at all time points. For both of these outcomes, the difference between groups diminished over time.

### b) Balloon kyphoplasty versus percutaneous vertebroplasty

Six RCTs<sup>(25,27,28,31,32,34)</sup> (five unique trials,  $n = 857$ ) and one quasi-randomized study ( $n = 112$ )<sup>(26)</sup> met eligibility criteria. Two trials were single-blinded,<sup>(32,34)</sup> two trials were unblinded,<sup>(25,31)</sup> and two trials had no blinding specified.<sup>(26–28)</sup> Treatment allocation was performed by computerized block randomization in two studies,<sup>(25,27,28)</sup> assigned by the operating surgeon in two studies,<sup>(26,34)</sup> and was not specified in two studies.<sup>(31,32)</sup> Follow-up duration ranged from 6 to 60 months.<sup>(27,28)</sup>

The mean participant age was 71.6 years, and 75% were female. Qualifying vertebral fractures were acute or subacute, often less than 2 months old<sup>(25–28)</sup> with some studies requiring supportive MRI findings.<sup>(25,26,32,34)</sup> Fractures were most commonly located near the thoracolumbar junction. Three studies limited participation to individuals who had failed several weeks of conservative therapy.<sup>(25,31,32)</sup> Three studies were limited to or mostly comprised participants with osteopenia or osteoporosis.<sup>(26,31,32)</sup> At baseline, participants reported severe back pain (mean VAS range 7.6–8.1),<sup>(25–28,32)</sup> substantial back-related disability (mean Oswestry Disability Index [ODI] range 58% to 66%),<sup>(25,26,32)</sup> and fair-to-poor quality of life (mean SF-36 PCS and EQ-5D approximately 28 and 0.42, respectively).<sup>(25)</sup>

Efficacy findings are as follows:

**Pain:** In two RCTs, statistically significant, but small and likely to be clinically unimportant, differences favored kyphoplasty over percutaneous vertebroplasty at 1 month (VAS mean difference =  $-0.28$  [ $-0.43, -0.13$ ;  $n = 107$ ,  $k = 1$  trial])<sup>(32)</sup> and percutaneous vertebroplasty over kyphoplasty at 5 years (mean difference:  $0.60$  [ $0.09, 1.11$ ];  $n = 100$ ,  $k = 1$  trial),<sup>(27)</sup> with no statistically significant differences at other time points.<sup>(21,24,29)</sup> In the quasi-randomized study, the mean difference in pain between treatments was  $0.60$  [ $0.22, 0.98$ ];  $n = 86$ ).<sup>(26)</sup>

**Disability:** In two RCTs<sup>(25,32)</sup> and one quasi-randomized study,<sup>(26)</sup> there were no statistically significant differences between treatments in improvement in ODI from baseline at any time points ranging between 3 months and 2 years.

**Quality of life:** There was no statistically significant difference in improvement in SF-36 PCS or EQ-5D between treatments at any time point.

### c) Balloon kyphoplasty versus KIVA®

Two eligible trials randomized participants to kyphoplasty versus KIVA®.<sup>(22,29)</sup> KIVA® is a proprietary system that uses a flexible implant made of a medical polymer to restore height to the vertebral body and hold the cement. Inserting the implant requires an incision about 1 cm in length, about the same size as with balloon

kyphoplasty. Studies were single-blinded using a bipedicular approach to surgery. Follow-up was 12 and 14 months, respectively. Mean participant age was 73.7 years (72.8% female).

Efficacy findings were in the areas of pain, disability, and quality of life. Treatment groups both had large improvements in back pain (VAS) and back-related disability (ODI). One study reported large improvements in both groups in quality of life (SF-36 PCS).<sup>(22,29)</sup> However, there were no differences in the magnitude of improvement in any of these outcomes at any time point. There was no difference in risk of incident radiographic vertebral fractures or incident adjacent radiographic vertebral fractures after kyphoplasty versus KIVA®.<sup>(22,29)</sup> There was no difference in serious AE between kyphoplasty and KIVA® participants up to 12 months (34.6% versus 28.6%; 1.21; 0.84, 1.75; events = 80;  $n = 253$ ).<sup>(22,29)</sup>

#### d) Balloon kyphoplasty versus vertebral body stenting

One eligible trial ( $n = 63$ , 100 treated levels) randomized participants to kyphoplasty versus vertebral body stenting, reporting only there were no neurologic sequelae in the immediate postoperative period.<sup>(21)</sup>

#### Summary of balloon kyphoplasty

On average, individuals with painful vertebral fracture experienced statistically significant symptomatic improvement compared with baseline with all studied treatment interventions, including nonsurgical management. Though we found that kyphoplasty was associated with improved pain, back-related disability, and quality-of-life outcomes compared with nonsurgical management, these results were derived almost entirely from a single trial. Further, the magnitude of improvement from baseline in these outcome measures after kyphoplasty relative to nonsurgical management appeared to diminish over time, and the mean between-group differences were smaller than previously reported minimally clinically important differences for individuals, raising concerns about their clinical significance. Because we identified no eligible trials of kyphoplasty versus sham kyphoplasty, it was not possible to determine to what extent the observed improvements of kyphoplasty versus nonsurgical management were attributable to a sham effect.

Compared with either percutaneous vertebroplasty or KIVA®, there was no significant difference in pain, back-related disability, or quality-of-life outcomes, although reductions in kyphotic and increases in vertebral height were greater with kyphoplasty compared with percutaneous vertebroplasty. These results were limited by the lack of results reporting the proportion of participants in each treatment group that experienced a clinically important difference in each efficacy outcome. The high risk of bias ratings of all the trials comparing kyphoplasty versus percutaneous vertebroplasty further limits confidence in these findings.

The current review was limited by available evidence. Though 10 unique trials met eligibility criteria, after considering the different kyphoplasty treatment comparisons, outcome measures, and time points, only relatively few participants ultimately provided information about the efficacy and safety of kyphoplasty versus other interventions. Second, because all but two trials reported results for efficacy outcomes only as overall group means,<sup>(22,29)</sup> it was difficult to determine how many and which types of participants achieved clinically meaningful improvements with treatment. Third, AE and

incident vertebral fractures were rarely systematically reported and often were not reported at all. Fourth, most trials were rated as having high risk of bias, most commonly due to lack of blinding of participants and/or outcome assessors and less often due to a lack of allocation concealment, both which could have led to overestimation of the true effect of interventions.

In summary, in middle-aged and older adults with vertebral fracture on the basis of one study, kyphoplasty was associated with greater improvement in pain, disability, and quality of life than was nonsurgical management. Based on a small number of heterogeneous (and high risk of bias) studies, there were no differences in these outcomes between kyphoplasty and either percutaneous vertebroplasty or KIVA. Any apparent benefits of kyphoplasty over nonsurgical management appeared to decrease over time, and, based on available data, it was not possible to determine whether these between-group differences were clinically meaningful or the extent to which they were accounted for by sham effects or study bias.

#### Key Questions 3 and 4. What are the harms of vertebral augmentation therapy, including possible risk of new vertebral fractures?

**Recommendation/finding:** Potential harms and serious AE associated with vertebral augmentation therapy include risk of death, incident vertebral fracture, cement leakage, adjacent fractures, vasovagal reactions, cord compression requiring immediate decompression, hypoxia, and respiratory failure. It is uncertain whether or not vertebroplasty increases risk of incident or radiographic vertebral fractures or serious AE related to percutaneous vertebroplasty due to a low number of events and the potential for bias. It is uncertain whether kyphoplasty increases risk of incident or radiographic vertebral fractures or serious AE related to kyphoplasty, despite case reports, due to a lack of high-quality evidence.

**Quality of evidence:** Low for percutaneous vertebroplasty; low for kyphoplasty

**Strength of recommendation/finding:** Moderate for percutaneous vertebroplasty; weak for kyphoplasty.

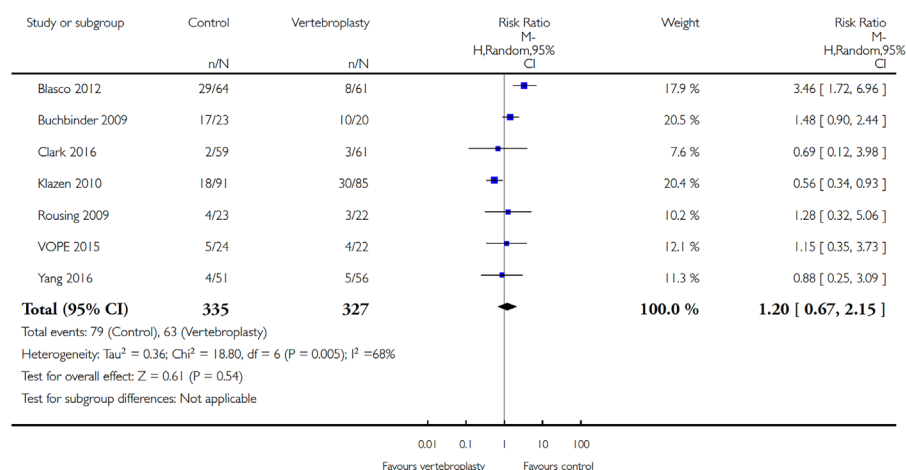
#### Evidence in support of recommendation/finding

##### 1. Percutaneous vertebroplasty

##### a) Harms associated with percutaneous vertebroplasty for new clinically or radiologically apparent vertebral fractures

Based upon low-quality evidence from six trials (control was placebo for one trial and usual care for the other trials) with up to 12 to 24 months of follow-up, it is not certain whether percutaneous vertebroplasty increases the risk of new symptomatic vertebral fractures (48 fractures in 418 participants (pooled incidence 95 per 1000; range 34 to 264) observed in the percutaneous vertebroplasty group compared with 31 fractures in 422 participants (pooled incidence 73 per 1000) in the control group (RR 1.29 [95% CI 0.46 to 3.62]).<sup>(5,35,36)</sup> There was substantial statistical heterogeneity ( $I^2 = 70\%$ ).

Based upon eight trials (placebo control in four trials and usual care in four trials), it is also not certain whether vertebroplasty increases the risk of new radiographic vertebral fractures (vertebroplasty: 110 fractures in 411 participants (26.8%);



**Fig. 4.** Forest plot of the safety outcome: vertebroplasty versus placebo (sham) or usual care, new radiographic vertebral fractures<sup>5</sup>.

control: 93 fractures in 393 participants (23.7%); RR 1.14 (95% CI 0.71 to 1.84). There was also substantial heterogeneity for this analysis ( $I^2 = 67\%$ ) (Fig. 4).

## b) Other serious AE reported with percutaneous vertebroplasty

Based upon a pooled analysis of five trials (placebo control in three trials and usual care in two trials), there were no significant between-group differences in the number of other serious adverse events (vertebroplasty: 16/408 [34 per 1000, range 18 to 62], control: 23/413; RR 0.61 [95% CI 0.33 to 1.10]). Excluding one of the vertebroplasty versus usual care trials that reported serious adverse events that appeared unrelated to the treatment (ie, depression, pneumonia, sleep disturbance), the RR became 1.26 (95% CI 0.41 to 3.88). Serious AE related to percutaneous vertebroplasty were reported in several trials. These included osteomyelitis requiring surgical drainage, rib and pedicle fractures, thecal sac injury, vasovagal reactions, acute asthma exacerbation, cord compression requiring immediate decompression, hypoxia, and respiratory failure. Cement leakage was also reported to occur frequently (up to 78% of cases), but it was not possible to determine the rate of significant sequelae arising from cement leakage or embolism because of the small number of events. Although most cases were asymptomatic, one trial<sup>(15)</sup> reported an instance of cement leakage into the epidural space requiring immediate decompression.

## Summary of percutaneous vertebroplasty

Although the updated Cochrane review did not demonstrate an increased risk of incident symptomatic vertebral fractures or other serious AE associated with percutaneous vertebroplasty, clinically important increased risks cannot be excluded because of the small number of events.

## 2. Balloon kyphoplasty

### a) Kyphoplasty versus nonsurgical management

**Incident vertebral fractures:** There was no significant difference between kyphoplasty and nonsurgical management

groups with regard to the risk of new-onset radiographic vertebral fracture occurring at 3 months (21.9% versus 27.0%; RR = 0.81 [0.51, 1.29; events = 54;  $n = 223$ ]), 12 months (33.0% versus 25.3%; 1.31 [0.85, 2.02; events = 62;  $n = 220$ ]), or 24 months (47.5% versus 44.1%; 1.08 [0.81, 1.44; events = 101;  $n = 220$ ]). There was also no difference in incident adjacent radiographic vertebral fracture (23.7% versus 16.7%; 1.54 [0.89, 2.65; events = 45;  $n = 220$ ]) or incident clinical vertebral fracture (20.8% versus 17.9%; 1.07 [0.69, 1.68; events = 58;  $n = 300$ ]) at 24 months.<sup>(23,30,33,34)</sup>

**AE:** The FREE study reported a significantly increased risk of any AE occurring within 1 month after kyphoplasty compared with nonsurgical management (63.1% versus 36.4%; 1.73 [1.36, 2.21; events = 149;  $n = 300$ ]) but not within 24 months (89.9% versus 88.7%; 1.01 [0.94, 1.10; events = 268;  $n = 300$ ]).<sup>(23,30,33)</sup> There was no significant difference in risk of serious AE, either within 1 month (16.1% versus 11.3%; 1.43 [0.80, 2.55; events = 41;  $n = 300$ ]) or 24 months of the intervention (49.7% versus 48.3%; 1.03 [0.82, 1.29; events = 157;  $n = 300$ ]).<sup>(23,30,33)</sup>

### b) Kyphoplasty versus percutaneous vertebroplasty

**Incident vertebral fractures:** There was no statistically significant difference in risk of incident radiographic vertebral fracture between treatments occurring within 1 month (15.2% versus 17.9%; 0.85 [0.54, 1.33];  $n = 381$ ;  $k = 1$  trial),<sup>(25)</sup> at 3 months (23.3% versus 27.4%,  $p = 0.43$ ,  $k = 1$ ),<sup>(25)</sup> 12 months (22.3% versus 23.7%,  $p = 0.71$ ,  $k = 2$ ),<sup>(25,32)</sup> 24 months (49.1% versus 57.7%,  $p = 0.23$ ,  $k = 1$ ),<sup>(25)</sup> or 5 years (24.0% versus 20%,  $p > 0.05$ ,  $k = 1$ ).<sup>(27)</sup> Similarly, there was no significant difference in risk of incident adjacent radiographic vertebral fracture occurring after 12 months (11.3% versus 12.8%; 1.58 [0.79, 3.13];  $n = 278$ ;  $k = 3$ ),<sup>(27,28,31,32)</sup> and no significant difference in risk of incident clinical vertebral fracture at 1 month (4.7% versus 8.9%; 0.53 [0.24, 1.15]) and 2 years (15.2% versus 17.9%; 0.76 [0.52, 1.10]) in a single RCT,<sup>(25)</sup> or at 2 years in one quasi-randomized study (18.2% versus 14.3%, 1.27 [0.48, 3.36],  $n = 86$ ).<sup>(26)</sup> Compared with percutaneous vertebroplasty, kyphoplasty also resulted in larger reductions in kyphotic angle at 30 days, at 12 months, and after 12 months. Vertebral height also increased to a greater extent

with kyphoplasty compared with percutaneous vertebroplasty (data not shown).

**AE:** Only one study reported data on AE and found no increased risk of AE at 30 days (0.70 [0.44, 1.11]; events = 63;  $n = 381$ ) or 2 years (1.09 [0.49, 2.40]; events = 23;  $n = 281$ ).<sup>(25)</sup>

### Summary of balloon kyphoplasty

Compared with nonsurgical management, kyphoplasty was not associated with a statistically significantly increased risk of incident vertebral fracture, though CIs were wide, and results could not exclude a clinically meaningful increase in risk. Further, compared with nonsurgical management, kyphoplasty was associated with a near doubling in risk of any AE within 30 days of intervention. Based on the mean between-group differences in efficacy outcomes of uncertain clinical importance, an increase in early AE, and the high risk of bias of the largest eligible kyphoplasty versus nonsurgical management trial, it is uncertain whether any benefits of kyphoplasty versus nonsurgical management of vertebral fracture outweigh potential harms.

Compared with either percutaneous vertebroplasty or KIVA, there was no significant difference in risk of incident vertebral fracture or risk of any AE or serious AE with KP, although reductions in kyphotic and increases in vertebral height were greater with kyphoplasty compared with percutaneous vertebroplasty. These results were limited by wide CIs around the estimates for risk of incident vertebral fracture that could not exclude clinically important differences in fracture risk and limited reporting of AE outcomes. The high risk of bias ratings of all the trials comparing kyphoplasty versus percutaneous vertebroplasty further limits confidence in these findings.

A previous biased study reported on the incidence of new vertebral fractures with uncertain results and, when compared with other surgical techniques, kyphoplasty was associated with similar reductions in pain.<sup>(37,38)</sup> Because kyphoplasty is an invasive procedure, there is concern that kyphoplasty may increase the risk of new vertebral fractures at operated and adjacent levels.<sup>(39)</sup> Adjacent fractures are reported to occur earlier than new-onset fractures at the treated level (55 versus 127 days) with a RR of 4.62.<sup>(38)</sup> However, when kyphoplasty and percutaneous vertebroplasty were compared, there was no significant difference in incidence of new-onset vertebral fractures.<sup>(37,39–41)</sup> Kyphoplasty is associated with a 9% (81 in 1000 fracture level-years) risk of epidural cement leakage, which may cause nerve-root injury.<sup>(42)</sup> We showed a similar risk of AE (including cement leaks) and serious AE in kyphoplasty and percutaneous vertebroplasty.

In summary, the current review was limited by available evidence. AE and incident vertebral fractures were rarely systematically reported and often were not reported at all. In middle-aged and older adults with vertebral fracture on the basis of one study, kyphoplasty was associated with an increase in risk of early AE than was nonsurgical management. Based on a single study, there was no difference in AE between kyphoplasty and percutaneous vertebroplasty. Risks of subsequent fracture were not statistically significantly different between kyphoplasty and other treatments, but these results could not rule out important differences.

### 3. Meta-analyses of vertebroplasty and kyphoplasty

Two recent meta-analyses examined the incidence of new vertebral fractures after both vertebroplasty and kyphoplasty.

The first included 871 patients from seven randomized controlled trials, of whom 436 received vertebral augmentation treatment.<sup>(43)</sup> Numbers of new vertebral fractures in the two groups were not significantly different. Six studies reported on new adjacent vertebral fractures. As heterogeneity was identified among studies, two subgroups were created and a small statistically significant increase in the incidence of new adjacent vertebral fractures was found in the larger subgroup, which comprised European trials. The second study included 1328 patients from 12 randomized controlled trials, clinical controlled trials, and prospective clinical studies, of whom 768 received vertebral augmentation treatment with either percutaneous vertebroplasty or kyphoplasty.<sup>(44)</sup> No increases in the incidence of either new vertebral or new adjacent vertebral fractures compared with nonoperative management were found.

### Key Questions 5 and 6. What is the efficacy and safety of other nonpharmacologic treatments, such as spinal bracing and exercise interventions after vertebral fracture?

**Recommendation/finding:** For patients with painful vertebral fractures, there is limited evidence that spinal bracing improves physical function, disability, or quality of life. Exercise interventions can improve mobility, and may improve pain, fear of falling, and back extensor strength in individuals with vertebral fractures.

**Quality of evidence:** Low for bracing; low for exercise interventions.

**Strength of recommendation/finding:** Weak for bracing; weak for exercise interventions.

### Evidence in support of recommendation/finding

There have been no trials comparing vertebral augmentation with other nonsurgical interventions.

### 3. Spinal orthoses

Characteristics and outcomes of trials included in the analysis are summarized in Table 4. Safety and efficacy findings are as follows:

**Pain:** All four studies reported pain outcomes with improved pain over time, but no trials suggested benefit between the different types of braces used. In Pfeiffer and colleagues,<sup>(45)</sup> there were no between-group differences in pain, but it should be noted that the age of the vertebral fracture was not known. Pfeiffer and colleagues<sup>(46)</sup> studied patients with vertebral fracture diagnosed in the past 6 months and reported 38% reduction in pain in the orthosis versus control groups. In the setting of acute vertebral fracture, Kim and colleagues<sup>(47)</sup> reported no significant change in VAS for pain in the control versus either treatment group comparing a soft brace to a rigid thoracolumbarsacral orthosis brace at 2, 6, and 12 weeks after initiation of the bracing, though there was a trend toward pain improvement in the rigid brace group. Li and colleagues<sup>(48)</sup> reported significant improvements in pain in both orthoses groups compared with control, but there were no significant differences between the orthoses groups.

**Disability/function:** Kim and colleagues<sup>(47)</sup> studied the effects of 8 weeks of bracing on ODI and reported no significant



**Table 4.** Characteristics and Outcomes of Studies Examining Spinal Orthoses for Fracture Management

Author, publication, date, setting	Patient characteristic	Concomitant therapy	Design	Major outcomes and limitations
Kim et al., 2014 Tertiary care, teaching hospital	Enrolled 0–3 days after clinical OVF. Age $\geq 50$ years. Total randomized: 60 patients; 41 female. Acute single fracture. Exclusion: $>2$ recent fracture.	BAM not described. Exercise: advice-injury avoidance; allowed to walk as desired	1:1:1 allocations. Control, soft brace, rigid TSLO brace (How Medicare, Seoul, Korea). 8-week continuous brace use except when lying down. Primary outcome: change in ODI at 12 weeks. Secondary outcomes: change in VAS Pain Score and in anterior vertebral compression.	No significant change at 12 weeks in ODI for control versus either or soft brace. No significant change in VAS for pain or in vertebral body compression ratio for control versus either treatment group. Results potentially confounded by higher baseline ODI score for the rigid brace group compared with control and soft brace group. There appears to be a trend toward improvement for ODI and pain in the rigid brace group.
Li et al., 2014 Inpatient ward, teaching hospital	All subjects fitted with custom-molded TSLO for first week after acute OVF for 24 hours per day. Age $\geq 55$ years, mean age 82. All female. Total randomized: 51. Cumulative fractures. 25 subjects with one fracture, 16 with 2 fractures, 10 with 3 or more fractures. Exclusion: prior spine surgery or severe spine DJD.	BAM not described. Exercise protocol not described.	Randomized starting at week 1 to either soft lumbar orthosis or Spinomed orthosis (MediBayreuth). Spinomed orthosis worn 3 hours daily with soft orthosis at other times. Outcomes rated at end of week 1 (baseline) and week 3: VAS pain score, gain in functional mobility (FIM-motor scores), EMS, Modified Functional Ambulation Category. Thoracic kyphosis measured by X-ray.	Improvement in all pain and functional scores between baseline and week 3. No significant difference between soft lumbar brace and Spinomed groups. No difference in kyphosis angle between groups (only 5 subjects in each group measured).
Pfeifer et al., 2011 Ambulatory, community dwelling. Recruited through newspaper advertisement. Planned RCT crossover study; protocol revised at 6 months.	One OVF within the past 6 months and kyphosis angle $>60$ degrees. Age $\geq 60$ years, Mean age $\sim 72$ . All female. Average of $\sim 2$ vertebral fractures. Total randomized: 108. Exclusion: severe spinal DJD.	BAM not described. Exercise protocol not described.	1:1:1 allocation among control, Spinomed, and Spinomed Active brace (body suit with posterior support rod). Brace worn 2 hours per day. Originally planned crossover at 6 months. Treatment groups refused due to perceived efficacy and continued to 12 months. Control group started Spinomed brace at 6 months to completion.	At 6 months, both brace groups compared with control showed significant improvement in back extensor muscle strength and abdominal flexor strength (measured by Digi-Max, mechaTronic, Germany), body sway, kyphosis angle, FEV1, pain perception, and QoL. No difference between brace types. Nonsignificant trend to further improvement at 12 months.
Pfeifer et al., 2004 Ambulatory, community dwelling. Prospective randomized controlled	One or more vertebral fractures. Enrollment from time of fracture: not specified. Angle of	BAM: All participants received calcium, vitamin D supplement, and bisphosphonate.	Participants randomized to control or Spinomed orthosis for 6 months. Orthosis to be worn 2	At 6 months, statistically significant improvement in isometric back extensor muscle



**Table 4.** (Continued)

Author, publication, date, setting	Patient characteristic	Concomitant therapy	Design	Major outcomes and limitations
crossover trial (crossover not done because of participant refusal). Recruitment by newspaper advertisement.	kyphosis $\geq 60$ degrees. All females aged $\geq 60$ years, mean age 72. Total randomized: 62. Exclusion: advanced spinal DJD.	Exercise protocol not specified.	hours daily. Planned crossover not done at 6 months because of participant refusal. Control group switched to orthosis at 6 months. Measurements as in Pfeifer et al., 2011.	strength, abdominal flexor strength, angle of kyphosis, body sway and sway velocity, FEV1, and VC. Also improvement compared with control in pain relief, self-care, and well-being. Additional improvement at 12 months in back extensor muscle strength and abdominal flexor strength. Trend to improvement in angle of kyphosis, VC, pain, and limitations in daily living.

BAM = bone-active medication; DJD = degenerative joint disease; EMS = Elderly Mobility Scale; FEV1 = forced expiratory volume in 1 second; FIM = Functional Independence Measure; OVF = osteoporotic vertebral fracture; QOL = quality of life; RCT = randomized controlled trial; TLSO = thoracolumbosacral orthosis; VAS = visual analog scale; VC = vital capacity.

improvement at 12 weeks in either the rigid or soft brace group compared with control. However, the rigid brace group had a higher baseline ODI score than either the control or soft brace group, which may have confounded the results. Another study examined functional mobility pre- and post-bracing using Functional Independence Measure-Motor Scores, Elderly Mobility scale, and Modified Functional Ambulation Category and found that after 3 weeks of orthotic treatment, there was significant improvement in all measures of functional mobility but no difference between the Spinomed (Fig. 4) or soft lumbar orthosis groups.<sup>(47)</sup> In other studies that assessed limitations of daily living, there were improvements reported compared with the control group at 6 months that were no longer significant at 1 year.<sup>(45,46)</sup>

**Quality of life:** One study compared general quality of life with the SF-36 quality of life measure in the control (no brace), soft brace, and rigid brace groups.<sup>(47)</sup> There were no significant differences between the three groups for general health status derived from the SF-36 physical and mental component scores at 6 weeks and 12 weeks.

**Posture/kyphosis:** Pfeiffer and colleagues<sup>(45)</sup> reported a within-group reduction of  $7.9 \pm 4.9$  degrees in kyphosis in the bracing group versus a  $1.6 \pm 5.5$  degree reduction in kyphosis in the control group that was significantly different between groups at 6 months ( $p = 0.02$ ). The control group crossed over to wearing the brace at 6 months, and kyphosis reduced significantly at 12 months in this group by  $4.2 \pm 4.9$  degrees, but the first bracing group did not have any further improvement in kyphosis at 12 months ( $1.9 \pm 4.1$  degrees). In a later study, Pfeiffer and colleagues<sup>(46)</sup> reported, coincidentally, the exact same values as previously reported of a  $7.9 \pm 4.9$  degree improvement in now 36, instead of 31, patients, who were assigned to wear the Spinomed and an  $8.1 \pm 10.5$  degree improvement in 36 patients assigned the Spinomed Active brace, both values representing a significant within-group reduction in kyphosis angle measured from standing

photomorphometry at 6 months ( $p < 0.01$ ). After rigid bracing, there was no improvement in anterior/posterior vertebral height ratio at 12 weeks, after 8 weeks of rigid bracing.<sup>(47)</sup> Li and colleagues<sup>(48)</sup> described the effects of bracing on thoracic kyphosis angle measured as Cobb angle ( $T_5$  to  $T_{12}$ ) from lateral spine radiograph in a subset of 5 participants from each group: the pretreatment kyphosis angle averaged 33 degrees (range 18–58) and posttreatment was 30.5 degrees (range 15–50). However, these data are difficult to interpret, as one subject decreased kyphosis from 58 to 32 degrees and another subject increased kyphosis from 18 to 30 degrees, whereas 80% had either no or relatively little change (within 5 degrees).

**Performance measures:** No trials included measures of physical mobility, although two trials included postural sway outcomes.<sup>(45,46)</sup> One study reported significant differences between the bracing group and control at 6 and 12 months in body sway path length and velocity favoring the bracing group.<sup>(45)</sup> At 6 months, body sway path length (mm) reduced  $20.4 \pm 40.2$  mm in the intervention group versus  $1.7 \pm 35.6$  mm in the control group ( $p = 0.01$ ). At 12 months, significant differences favored the control group who had crossed over to wearing the brace, although the results were confounded because 10% of the subjects agreed to finish the 6-month intervention period, whereas the remaining 28 subjects (90%) continued wearing the orthosis and were essentially followed over an intervention period of 12 months total.

**Muscle strength/endurance:** One study compared muscle performance outcomes after use of Spinomed and Spinomed active orthoses to controls.<sup>(46)</sup> Compared with controls, participants treated with either brace for 6 months had improvement in back extensor muscle strength (64% to 72%) and abdominal flexor strength (33% to 56%). With continued brace usage, no further improvement in strength or maintenance of improvement was observed at 12 months, leading the authors to conclude that the effects of bracing were best appreciated within the first 6 months of treatment.

**Falls:** No trial reported falls outcomes.

**Global satisfaction with intervention:** Only one study<sup>(47)</sup> examined satisfaction with treatment during the follow-up assessments and reported no differences among the three groups ( $p = 0.42$ ).

**AE:** No AE were reported in three of the four bracing trials. In one study,<sup>(46)</sup> AE were not specifically reported, but 5 women dropped out of the study because of either continued pain or "low comfort."

**Risk of bias:** One study was rated as unclear risk of bias due to inadequate reporting of randomization, attrition, protocol, and blinding procedures; one study was rated as low risk; and two as high risk of bias. Blinding of participants was not possible for any trials due to the nature of the intervention.

#### 4. Exercise

Efficacy and safety findings are as follows:

**Pain:** Of the nine trials, four examined treatment effects in the short term, ranging from 4 to 22 weeks, and results were mixed. Exercise had no significant effect on pain outcomes after 4 weeks.<sup>(49)</sup> However, after a 10-week multimodal physical therapy intervention that included exercise, Bennell and colleagues<sup>(50)</sup> reported a significant clinically meaningful between-group difference in favor of the intervention for pain on movement (mean change score  $-1.8$  points [95% CI  $-3.5$  to  $-0.1$ ],  $p < 0.05$ ) and pain at rest (mean change score  $-2.0$  points [95% CI  $-3.8$  to  $-0.2$ ],  $p < 0.05$ ). Similarly, Wang and colleagues<sup>(51)</sup> reported a significant, but likely to be not clinically meaningful, between-group difference in favor of the intervention for pain (mean between-group difference in change scores versus control  $-0.52$ ,  $p = 0.001$ ) after 4 weeks. One study reported that supervised exercises for 10 weeks assessed at all time points (5 weeks, 10 weeks, 22 weeks) demonstrated "a significant difference between the course of values from the two study groups ( $p = 0.02$ )."<sup>(52)</sup> However, when these results were reanalyzed by the systematic review team as intention-to-treat analysis, no significant effect on pain was observed at 4 weeks, but only at 10 weeks was there a significant difference between groups in favor of the intervention group for pain (mean between-group change score  $-1.03$  points [95% CI  $-1.37$  to  $-0.69$ ],  $p = 0.013$ , not considered significant if using a Bonferroni correction of six).

Similarly, conflicting data were observed for the two longer-term studies that reported pain as an outcome with follow-up ranging from 6 months to 2 years. For pain with activities, no significant between-group difference was observed in 185 women with an average age of 81 who were enrolled based upon having  $\geq 1$  vertebral fracture.<sup>(53)</sup> However, in a trial of 138 women aged in the late 60s, there was a reported significant between-group difference in favor of the intervention for pain after 24 weeks (mean between-group difference in change scores versus control  $-0.72$  points,  $p = 0.001$ ), and after 52 weeks (mean between-group difference in change scores versus control  $-1.28$  points,  $p = 0.001$ ).

**Disability/function:** In general, shorter-term studies did not report significant improvements in overall self-reported function, but there were small effects in some of the subscale

measures. For example, Bennell and colleagues<sup>(50)</sup> reported no between-group difference in activity restriction but did report a significant improvement in the physical function subscale of the QUALEFFO-41 (mean between-group difference in change scores  $-4.8$  points [95% CI  $-9.2$  to  $-0.5$ ],  $p < 0.05$ ) on a 0 to 100 scale, where lower scores indicate better physical function. However, in a larger study of 89 women, there was no significant improvement in the physical function subscale of the QUALEFFO-41.<sup>(54)</sup> Two other studies reported no significant effect of exercise after 4<sup>(52)</sup> and 10 weeks<sup>(51)</sup> on self-reported physical function using the ODI or the Oswestry Low Back Pain Questionnaire, respectively.

When examining the studies with longer follow-up of up to 2 years, there is a suggestion that the exercise interventions may exert long-range effects that are not initially appreciated. For example, in one study, there was no significant effect of exercise at 6 months for physical function or activities of daily living subscales of the Osteoporosis Quality of Life Questionnaire (OQLQ), but after 12 months, between-group differences in the activities of daily living subscale of the OQLQ were significant.<sup>(55)</sup> Another study favoring the exercise intervention group reported a significant effect of exercise on the physical function subscale of the QUALEFFO-41 at 1-year follow-up (mean change score  $-2.5$  points [95% CI  $-5.0$  to  $-0.03$ ] for the intervention group versus  $-1.0$  point [95% CI  $-1.5$  to  $3.4$ ] for the control group, effect size 0.3,  $p < 0.047$ ).<sup>(54)</sup> Wang and colleagues<sup>(51)</sup> also reported a significant between-group difference in favor of the intervention for self-reported physical function using the ODI after 6 and 12 months. Finally, a recent study reported that the exercise intervention led to a significant improvement in some subscales of the QUALEFFO-41 questionnaire, including jobs around the house subscale and mobility subscale, but no change in activities of daily living subscale.<sup>(56)</sup> In summary, these data suggest inconsistent benefits from small effects.

**Quality of life:** As was observed for functional outcomes, similar results were observed favoring exercise interventions but only upon longer follow-up times. After only 4 to 12 weeks of exercise, most trials report no significant between-group differences in total scores or subscales from disease-specific quality of life outcomes,<sup>(50,54)</sup> with the exception of changes to physical function subscale<sup>(50)</sup> or mental function subscale.<sup>(54)</sup> The longer-term studies<sup>(55)</sup> reported significant improvements in symptom, emotion, and leisure/social subscales, and the differences in symptoms subscale persisted at 12 months. Bergland and colleagues<sup>(54)</sup> reported a significant between-group difference in total QUALEFFO-41 scores at 12-month follow-up (mean change score  $-3.3$  points [95% CI  $-5.2$  to  $-1.3$ ] for the intervention group versus  $-0.4$  points [95% CI  $-2.0$  to  $-2.7$ ] for the control group, effect size 0.3,  $p < 0.019$ ). Evstigneeva and colleagues also found significant improvements ( $p < 0.001$ ) in the QUALEFFO-41 total score (mean change score  $-5.8$  points [95% CI  $-7.8$ ,  $-3.8$ ]) for the intervention group versus the control group (mean change score 3.1 points [95% CI 1.3, 4.9]) and for pain, social function, and general health perception subscales after 12 months of exercise.<sup>(56)</sup> In summary, these data suggest inconsistent benefits from small effects.

Only three studies used generic health-related quality-of-life scales. Most report no significant between-group differences,<sup>(50,55)</sup> with the exception of one study,<sup>(54)</sup> which reported a significant between-group difference for General Health

Questionnaire total score (mean change score  $-3.7$  points for the intervention group [95% CI  $-5.5$  to  $-1.9$ ] versus  $-0.2$  points for the control group [95% CI  $-2.1$  to  $1.7$ ], effect size  $0.4$ ,  $p < 0.009$ ).

**Posture/kyphosis:** Three trials reported that exercise had no statistically significant effect on posture outcomes.<sup>(50,56,57)</sup> No other trials reported posture outcomes.

**Performance measures:** Several studies reported improved mobility and balance after an exercise intervention. In one, 3 months of exercise improved maximum walking speed over 20 meters (mean change score  $-1.3$  seconds [95% CI  $-2.0$  to  $-0.6$ ] for the intervention group versus  $0.6$  seconds [95% CI  $-0.3$  to  $1.4$ ] for the control group, effect size  $0.5$ ,  $p < 0.001$ ), a finding that persisted 9 months after cessation of intervention ( $p < 0.019$ ).<sup>(54)</sup> Other findings included improvement in time to get up from a supine position (mean time  $4.87$  seconds [SD =  $1.17$ ] for the intervention group versus  $7.73$  seconds [SD =  $1.65$ ] for the control group,  $p < 0.001$ ),<sup>(49)</sup> and improved Timed Up and Go test, where data from three trials were pooled in a meta-analysis, revealing a between-group difference of  $-1.09$  seconds (95% CI  $-1.78$  to  $-0.40$ ,  $p = 0.002$ ) in favor of exercise.<sup>(49,50,54)</sup> Because Bennell and colleagues<sup>(50)</sup> used a multimodal intervention, the meta-analysis was also performed excluding data from this trial, and the findings were similar. Discordant findings with respect to effects of longer-term exercise programs on Timed Up and Go performance exist. For example, whereas Evstigneeva and colleagues<sup>(56)</sup> reported a significant improvement in Timed Up and Go test performance (mean change score of  $-0.65$  seconds [95% CI  $-1.31$ ,  $-0.10$ ] for intervention group versus a mean change score of  $0.29$  seconds [95% CI  $-0.37$ ,  $0.95$ ] for control group,  $p = 0.020$ ), these data were not included in the meta-analysis because of the large difference in follow-up time. However, Papaioannou and colleagues<sup>(55)</sup> reported no significant between-group differences for Timed Up and Go test performance at 6 or 12 months. Data from this trial were not included in the meta-analysis because the required parameters were not available in the report or from the authors.

Estimates of the effect of exercise on measures of balance are limited. No significant effect of exercise on postural sway was observed after 22 weeks.<sup>(58)</sup> Functional reach was improved (mean change score  $1.7$  cm [95% CI  $0.1$  to  $3.1$ ] after 3 months of exercise for the intervention group versus  $-2.2$  cm [95% CI  $-3.8$  to  $-0.7$ ] for the control group, effect size  $= 0.6$ ,  $p < 0.001$ ), but it did not persist after cessation of intervention 9 months later.<sup>(54)</sup> After 6 months of exercise, tests of postural sway revealed a significant between-group difference in favor of exercise for the range of displacement during the eyes closed condition (mean change score  $-0.80$  cm [95% CI  $-1.45$  to  $-0.15$ ],  $p = 0.01$ ) but not for any of the other postural sway variables.<sup>(55)</sup> After 12 months, displacement in lateral and anteroposterior directions and velocity of movement (measured with a force plate) were significantly better in the intervention group compared with control ( $p < 0.01$ ), but no data were provided, and it is not clear if this is for the eyes open or eyes closed condition.<sup>(55)</sup> Evstigneeva and colleagues reported significant improvements in sit-to-stand weight transfer (mean change score  $-0.24$  seconds [95% CI  $-1.12$ ,  $0.64$ ] for the intervention group versus  $0.43$  seconds [95% CI  $0.13$ ,  $0.73$ ] for the control group,  $p = 0.010$ ) and tandem walk and sway tests (mean change score  $-0.08$  degrees/s [95% CI  $-1.62$ ,  $1.47$ ] for the intervention group versus  $1.72$  [95% CI  $0.15$ ,  $3.30$ ] for the control group,  $p = 0.029$ ).<sup>(56)</sup> However, no significant between-group differences were observed for

sit-to-stand left/right weight symmetry and weight-bearing squat tests.

**Muscle strength/endurance:** Exercise appears to improve back muscle strength or endurance, as it is a consistent finding in several studies, albeit not all of them. Bennell and colleagues<sup>(50)</sup> observed a significant effect of a multimodal physical therapy intervention including exercise for trunk muscle endurance (mean change score in Timed Loaded Standing test of  $46.7$  seconds [95% CI  $16.1$  to  $77.3$ ],  $p < 0.05$ ). In contrast, data from an abstract<sup>(59)</sup> using the study sample from Gold and colleagues<sup>(53)</sup> reported no between-group difference in change scores for trunk and arm muscle endurance. No effect of exercise on back extensor muscle strength was observed after 5 or 10 weeks;<sup>(58)</sup> however, another study reported a significant between-group difference in favor of exercise for trunk extension muscle strength after 6 months of exercise (between-group difference in change score  $10.68$  foot pounds [95% CI  $6.98$  to  $14.39$ ],  $p < 0.001$ ,  $n = 122$ , subgroup of total sample  $n = 185$ ).<sup>(53)</sup> Another study reported no significant difference in back extensor muscle strength when control and intervention groups were compared in intention-to-treat analyses ( $254 \pm 85$  N versus  $302 \pm 108$  N,  $p = 0.74$ ), but found a significant between-group difference in back extensor muscle strength ( $p = 0.029$ ) in a per-protocol analysis, where 8 individuals who dropped out or were not compliant with exercise or control activities were excluded, and adjustment was made for baseline differences.<sup>(57)</sup>

**Falls:** No trial reported falls outcomes. Olsen and colleagues<sup>(60)</sup> (an analysis of data from a prior trial<sup>(54)</sup>) reported a significant between-group difference in favor of the intervention group for Falls Self-Efficacy Scale-I score after 3 months and 12 months.

**Fractures and bone mineral density:** One study measured fractures as a secondary outcome,<sup>(56)</sup> although studies were not powered or designed with fracture as primary outcomes. During the 12-month study, 4 participants in the exercise group sustained clinical vertebral and nonvertebral fractures compared with 7 participants in the control group ( $p = 0.285$ ). Another study reported four fractures as AE during exercise or during assessments.<sup>(53)</sup> Effects of exercise interventions on bone mineral density are discrepant. Papaioannou and colleagues found no significant effect of thrice-weekly home exercise for 1 year on lumbar spine or femoral neck bone mineral density,<sup>(55)</sup> whereas Wang and colleagues<sup>(51)</sup> reported a significant between-group difference in favor of the intervention for lumbar bone mineral density (mean between-group difference in change scores versus control  $0.038$  g/cm<sup>2</sup>,  $p = 0.005$ ) after 52 weeks.

**AE:** No studies specifically indicated that AE were included as an outcome or described a method for assessing and recording AE throughout the trial. Adverse events were reported in the results section of four trials,<sup>(50,53,55–57)</sup> and one trial<sup>(52)</sup> indicated that there were five AE unrelated to study participation but did not describe them. Five events, including two fractures, were directly attributable to exercise (see above). Details are published elsewhere.<sup>(61)</sup>

**Risk of bias:** Four trials were rated as low risk of bias,<sup>(50,52–54)</sup> four as unclear risk of bias,<sup>(49,51,55,56)</sup> and one as high risk of bias.<sup>(57)</sup> Blinding of participants was not possible for any trials because of the nature of the intervention.

## Summary of nonpharmacologic interventions

Four studies of low quality considered spinal bracing after vertebral fracture in both acute and chronic settings. Evidence that spinal bracing affected rate of incident vertebral fracture was lacking. Three trials suggested backpack thoracolumbar orthosis, lumbosacral orthosis, or a garment orthosis worn 2 hours a day may reduce self-reported pain at 6 months, and the choice of orthosis did not matter. Backpack thoracolumbosacral orthosis and a garment orthosis may benefit trunk muscle strength and reduce thoracic kyphosis at 6 months. There is no evidence that spinal bracing improves quality of life, physical function, or disability.

Although there was substantial variability in study designs and interventions, the current evidence suggests that exercise interventions have significant positive effects on mobility and may improve pain, fear of falling, and back extensor strength. However, the magnitude of effects on mobility was small (eg, between-group differences approximately 1 second for Timed Up and Go and approximately 2 seconds for walking speed). Improvements in back extensor strength or endurance was reported across several trials, but no trials reported improvements in posture. However, available data are limited. Trials that had pain as an inclusion criterion reported significant reductions in pain with exercise, a finding that should be interpreted with caution given the lack of blinding of participants and self-reporting. Exercise may have an effect on disease-specific quality-of-life outcomes but only among interventions that were longer than 12 weeks in duration. Fractures attributable to either intervention or assessment occurred, but some were during transitions and not the exercises, indicating individuals with vertebral fractures need to learn how to safely perform both the exercises and transitions between exercises.

### Key Question 7. What research is needed to fill knowledge gaps to improve patient outcomes in managing osteoporotic vertebral fractures, either through vertebral augmentation or other nonpharmacologic approaches?

**Recommendation/finding:** General and intervention-specific research recommendations stress the need to reduce study bias and address methodological flaws in study design and data collection. This includes the need for larger sample sizes, inclusion of a sham control, more data on serious AE, and more research on nonpharmacologic interventions.

Several suggestions for future research are listed below, organized by general recommendations that apply to all studies, and then recommendations specific to studies of percutaneous vertebroplasty, balloon kyphoplasty, and bracing or exercise.

#### General recommendations for all future studies

- Future trials should identify other novel and potentially useful interventions for pain after vertebral fracture.
- Future trials should ensure adequate sample sizes to answer the research question.
- Future trials should have inclusion criteria that allow generalizable conclusions to be drawn.

- Include cost-effectiveness outcomes.
- Include anti-osteoporosis therapy as part of interventions.
- Patient registries may be helpful for widespread systematic data collection for safety after vertebral augmentation.
- More trials are needed exploring exercise or rehabilitation interventions in the acute/subacute stage after vertebral fracture.
- De-implementation of vertebroplasty to reduce any potential harms of the procedure should be considered by translating evidence into changes in practice and policy.
- All future studies should consider including outcomes important to people with osteoporotic spine fracture(s), health care providers, or health systems, such as quality of life, pain, falls, fractures, and disability.
- Future trials should include men.
- Future studies should consider the relative benefit of short-term versus long-term improvements. If short-term improvements are substantial, this might be sufficient to warrant the treatment even if long-term outcomes are similar. Impact of the intervention on disability also should be considered over the short term and long term.
- Registries should be established to systematically collect safety data on patients treated with vertebral augmentation.
- More trials are needed exploring exercise or rehabilitation interventions in the acute/subacute stage after vertebral fracture.

#### Percutaneous vertebroplasty

- No further trials of vertebroplasty should be performed, unless they are adequately powered to alter the conclusions of the current body of evidence that concludes that the procedure is no more effective than placebo and the benefits are unlikely to outweigh any harms of the procedure.
- Potential participants in any further trials of these procedures should be fully informed about the current body of evidence.
- Ethics committees should also be fully informed about the current body of evidence to inform their decision about the ethics of any further trials.
- All future trials should include strategies designed to minimize the potential for bias, including adequate allocation concealment, use of a realistic placebo intervention, and blinding of both participants and investigators to the intervention.
- Future trials should carefully characterize the timing and severity of vertebral fracture among study participants.

#### Balloon kyphoplasty

- Any further trials of kyphoplasty should have a placebo control group.
- Further studies are needed to resolve whether kyphoplasty increases the risk of future vertebral fractures or serious AE, which should be systematically collected.
- All future trials should include strategies designed to minimize the potential for bias, including adequate allocation concealment, use of a realistic placebo intervention, and blinding of both participants and investigators to the intervention.
- Future trials should carefully characterize the timing and severity of vertebral fracture among study participants.



## Bracing/exercise

- More research is needed in nonpharmacological interventions in general, including more clearly defined participant selection criteria and study protocols (including the frequency, intensity, time from acute vertebral fracture, number of vertebral fractures, and type of intervention used).
- More rigorous trial design is needed to reduce bias potential and improve adherence and attrition.
- More data are needed on serious AE in the intervention and compactor groups to ensure that harms of a nonpharmacological intervention do not outweigh any benefits.
- Few trials examine the efficacy of exercise after acute vertebral fracture, so this is an area where more research is needed.
- Future studies assessing the efficacy of nonpharmacological interventions should clearly define:
  - The type of brace (for bracing studies).
  - The frequency, intensity, time, and type of exercise(s) prescribed; therapeutic goals; physical therapy interventions; and methods of delivery (for exercise or physical therapy interventions).
- Future exercise trial design should account for low adherence and attrition in sample size calculations. Adherence appears to be higher among studies that include supervised, patient-specific assessment and prescription, even if it is intermittent.

## Guidance for clinical management of patients with acute vertebral fracture

### Recommendations/finding:

- The optimal management of vertebral fracture is uncertain. Routine use of vertebral augmentation is not supported by current evidence. When it is offered, patients should be fully informed about the evidence.
- Anti-osteoporotic medications must be initiated as soon as practicable, or continued, in patients with a recent vertebral fracture. A change in treatment may also need to be considered if the vertebral fracture occurred after 12 months from initiation of anti-osteoporotic treatment.
- Use of bracing in reducing pain immediately after vertebral fracture is not supported by current evidence.
- Exercise may improve mobility and may reduce pain and fear of falling. However, the use of exercise to improve other outcomes, including falls and fractures, is not supported by current evidence.

Based on the recommendations and findings in this report, the ASBMR Task Force offers the following guidelines for the clinical management of patients with vertebral fracture.

### Vertebral augmentation

- In the majority of patients, pain from a vertebral fracture diminishes with time. **Based on the available evidence, in patients with acutely painful vertebral fractures, percutaneous vertebroplasty provide no demonstrable clinically significant benefit over placebo or sham procedure.**

- **As head-to-head trials have not found significant benefits of kyphoplasty over vertebroplasty with respect to pain, disability, or quality of life, it is unlikely that kyphoplasty would have benefits over placebo, but no placebo-controlled trials of kyphoplasty have been performed.**
- **The optimal management of patients with acute vertebral fracture remains uncertain.**
- **Routine use of vertebral augmentation for pain relief after vertebral fracture is not supported by current data.**
- **It is critical that anti-osteoporotic medications are started, continued, or changed (in the case of treatment failure) in patients with recent vertebral fracture.** Data from several randomized controlled trials indicate anti-osteoporosis medications reduce the risk of subsequent vertebral fractures by 40% to 70%.

## Bracing/exercise

- Only four randomized controlled trials of variable quality examined the effects of hard and soft types of bracing for individuals with vertebral fractures. **The benefits of wearing a rigid or soft bracing in the acute stage (3 to 12 weeks after acute vertebral fracture) are contradictory regarding pain and disability outcomes, making it difficult to recommend bracing in the acute phase. However, based upon limited evidence, there appears to be a benefit of bracing on pain and possibly other outcomes of spine strength, kyphosis angle, pulmonary volume, and quality of life from backpack thoracolumbar orthosis, lumbosacral orthosis, or a garment orthosis worn 2 hours a day over 6 months among individuals within 6 months of onset of a vertebral fracture.** The choice of orthosis does not matter.
- **The majority of studies of exercise in individuals with vertebral fractures have not recruited individuals with acute fractures, so the evidence is indirect.** Many of the exercise programs were center-based and supervised by a physical therapist; setting and level of supervision may influence adherence or outcomes.
- **Exercise may improve mobility and reduce pain and fear of falling in those who have pain due to vertebral fracture.** Individual trials did report benefits for some outcome measures, including physical function, balance, back extensor muscle strength, trunk muscle endurance, quality of life, bone mineral density, and fear of falling. These findings should be interpreted with caution given the small number of trials and the heterogeneity in the direction and estimates of effects.
- **All of the trials' exercise programs included muscle strengthening, and many included back extensor muscle exercises (targeting strength or endurance). Therefore, to achieve the potential benefits suggested by any of the trials, these should be included in the exercise prescription.** In the presence of pain due to vertebral fracture, it may be advisable initially to perform exercises targeting back extensors or spine stabilizers in an unloaded position, such as supine, and then progressing the difficulty of the exercise according to tolerance. Examples include unilateral thoracic extension via supine shoulder flexion 180 degrees; gentle "press" of shoulders into floor while lying supine; or lumbar extension via unilateral activation of hip extensors pressing leg into floor while supine.



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## References

1. Melton LJ 3rd, Thamer M, Ray NF, et al. Fractures attributable to osteoporosis: report from the National Osteoporosis Foundation. *J Bone Miner Res*. 1997;12(1):16–23.
2. Strom O, Borgstrom F, Kanis JA, et al. Osteoporosis: burden, health care provision and opportunities in the EU: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos*. 2011;6:59–155.
3. Goz V, Errico TJ, Weinreb JH, et al. Vertebroplasty and kyphoplasty: national outcomes and trends in utilization from 2005 through 2010. *Spine J*. 2015;15(5):959–65.
4. Rodriguez AJ, Fink HA, Mirigian L, et al. Pain, quality of life, and safety outcomes of kyphoplasty for vertebral compression fractures: report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2017;32(9):1935–44.
5. Buchbinder R, Johnston RV, Rischin KJ, et al. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. *Cochrane Database Syst Rev*. 2018;(4):CD006349.
6. Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med*. 2009;361(6):557–68.
7. Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med*. 2009;361(6):569–79.
8. Clark W, Bird P, Gonski P, et al. Safety and efficacy of vertebroplasty for acute painful osteoporotic fractures (VAPOUR): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2016;388(10052):1408–16.
9. Firanescu CE, de Vries J, Lodder P, et al. Vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures (VERTOS IV): randomised sham controlled clinical trial. *BMJ*. 2018;361: k 1551.
10. Hansen EJ. A double-blind randomized clinical study comparing vertebroplasty with a SHAM procedure for acute osteoporotic vertebral compression fractures (VOPE). Thesis, University of Southern Denmark: Center for Spine Surgery and Research, Middelfart Hospital and Institute of Regional Health Research, University of Southern Denmark, Denmark; 2015.
11. Kroon F, Staples M, Ebeling PR, et al. Two-year results of a randomized placebo-controlled trial of vertebroplasty for acute osteoporotic vertebral fractures. *J Bone Miner Res*. 2014;29(6):1346–55.
12. Staples MP, Kallmes DF, Comstock BA, et al. Effectiveness of vertebroplasty using individual patient data from two randomised placebo controlled trials: meta-analysis. *BMJ*. 2011;343:d3952.
13. Blasco J, Martinez-Ferrer A, Macho J, et al. Effect of vertebroplasty on pain relief, quality of life, and the incidence of new vertebral fractures: a 12-month randomized follow-up, controlled trial. *J Bone Miner Res*. 2012;27(5):1159–66.
14. Chen D, An ZQ, Song S, Tang JF, Qin H. Percutaneous vertebroplasty compared with conservative treatment in patients with chronic painful osteoporotic spinal fractures. *J Clin Neurosci*. 2014;21(3):473–7.
15. Farrokhi MR, Alibai E, Maghami Z. Randomized controlled trial of percutaneous vertebroplasty versus optimal medical management for the relief of pain and disability in acute osteoporotic vertebral compression fractures. *J Neurosurg Spine*. 2011;14(5):561–9.
16. Klazen CA, Lohle PN, de Vries J, et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. *Lancet*. 2010;376(9746):1085–92.
17. Rousing R, Hansen KL, Andersen MO, et al. Twelve-months follow-up in forty-nine patients with acute/semiacute osteoporotic vertebral fractures treated conservatively or with percutaneous vertebroplasty: a clinical randomized study. *Spine (Phila Pa 1976)*. 2010;35(5):478–82.
18. Voormolen MH, Mali WP, Lohle PN, et al. Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study. *AJNR Am J Neuroradiol*. 2007;28(3):555–60.
19. Yang EZ, Xu JG, Huang GZ, et al. Percutaneous vertebroplasty versus conservative treatment in aged patients with acute osteoporotic vertebral compression fractures. *Spine (Phila Pa 1976)*. 2016;41(8):653–60.
20. Leali PT, Solla F, Maestretti G, Balsano M, Doria C. Safety and efficacy of vertebroplasty in the treatment of osteoporotic vertebral compression fractures: a prospective multicenter international randomized controlled study. *Clin Cases Miner Bone Metab*. 2016;13(3):234–6.
21. Werner CM, Osterhoff G, Schlickeiser J, et al. Vertebral body stenting versus kyphoplasty for the treatment of osteoporotic vertebral compression fractures: a randomized trial. *J Bone Joint Surg*. 2013;95(7):577–84.
22. Korovessis P, Vardakastanis K, Repantis T, Vitsas V. Balloon kyphoplasty versus KIVA vertebral augmentation—comparison of 2 techniques for osteoporotic vertebral body fractures: a prospective randomized study. *Spine (Phila Pa 1976)*. 2013;38(4):292–9.
23. Boonen S, Van Meirhaeghe J, Bastian L, et al. Balloon kyphoplasty for the treatment of acute vertebral compression fractures: 2-year results from a randomized trial. *J Bone Miner Res*. 2011;26(7):1627–37.
24. Borgstrom F, Olafsson G, Strom O, et al. The impact of different health dimensions on overall quality of life related to kyphoplasty and non-surgical management. *Osteoporos Int*. 2013;24(7):1991–9.
25. Dohm M, Black CM, Dacre A, et al. A randomized trial comparing balloon kyphoplasty and vertebroplasty for vertebral compression fractures due to osteoporosis. *AJNR Am J Neuroradiol*. 2014;35(12):2227–36.
26. Du J, Li X, Lin X. Kyphoplasty versus vertebroplasty in the treatment of painful osteoporotic vertebral compression fractures: two-year follow-up in a prospective controlled study. *Acta Orthopaedica Belgica*. 2014;80(4):477–86.
27. Liu JT, Li CS, Chang CS, Liao WJ. Long-term follow-up study of osteoporotic vertebral compression fracture treated using balloon kyphoplasty and vertebroplasty. *J Neurosurg Spine*. 2015;23(1):94–8.
28. Liu JT, Liao WJ, Tan WC, et al. Balloon kyphoplasty versus vertebroplasty for treatment of osteoporotic vertebral compression fracture: a prospective, comparative, and randomized clinical study. *Osteoporos Int*. 2010;21(2):359–64.
29. Tutton SM, Pflugmacher R, Davidian M, et al. KAST study: the Kiva system as a vertebral augmentation treatment—a safety and effectiveness trial: a randomized, noninferiority trial comparing the Kiva system with balloon kyphoplasty in treatment of osteoporotic vertebral compression fractures. *Spine (Phila Pa 1976)*. 2015;40(12):865–75.
30. Van Meirhaeghe J, Bastian L, Boonen S, et al. A randomized trial of balloon kyphoplasty and nonsurgical management for treating acute vertebral compression fractures: vertebral body kyphosis correction and surgical parameters. *Spine (Phila Pa 1976)*. 2013;38(12):971–83.
31. Vogl TJ, Pflugmacher R, Hierholzer J, et al. Cement directed kyphoplasty reduces cement leakage as compared with vertebroplasty: results of a controlled, randomized trial. *Spine (Phila Pa 1976)*. 2013;38(20):1730–6.
32. Wang CH, Ma JZ, Zhang CC, Nie L. Comparison of high-viscosity cement vertebroplasty and balloon kyphoplasty for the treatment of osteoporotic vertebral compression fractures. *Pain Physician*. 2015;18(2):E187–94.

33. Wardlaw D, et al. A randomized trial of balloon kyphoplasty and nonsurgical care for acute vertebral compression fracture. *Osteoporos Int*. 2009;20:5273–4.
34. Yi XD, Lu H, Tian F, et al. Recompression in new levels after percutaneous vertebroplasty and kyphoplasty compared with conservative treatment. *Arch Orthop Trauma Surg*. 2014;134(1): 21–30.
35. Staples MP, Howe BM, Ringler MD, et al. New vertebral fractures after vertebroplasty: 2 year results from a randomised controlled trial. *Arch Osteoporos*. 2015;10:229.
36. Trout AT, Kallmes DF, Kaufmann TJ. New fractures after vertebroplasty: adjacent fractures occur significantly sooner. *AJNR Am J Neuroradiol*. 2006;27(1):217–23.
37. Berlemann U, Franz T, Orler R, Heini PF. Kyphoplasty for treatment of osteoporotic vertebral fractures: a prospective non-randomized study. *Eur Spine J*. 2004;13(6):496–501.
38. Grafe IA, Da Fonseca K, Hillmeier J, et al. Reduction of pain and fracture incidence after kyphoplasty: 1-year outcomes of a prospective controlled trial of patients with primary osteoporosis. *Osteoporos Int*. 2005;16(12):2005–12.
39. Mudano AS, et al. Vertebroplasty and kyphoplasty are associated with an increased risk of secondary vertebral compression fractures: a population-based cohort study. *Osteoporos Int*. 2009;20(5): 819–26.
40. Xie W, Jin D, Wan C, et al. The incidence of new vertebral fractures following vertebral augmentation: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2015;94(37):e1532.
41. Zhang H, Xu C, Zhang T, Gao Z, Zhang T. Does percutaneous vertebroplasty or balloon kyphoplasty for osteoporotic vertebral compression fractures increase the incidence of new vertebral fractures? A meta-analysis. *Pain Physician*. 2017;20(1):E13– E28.
42. Taylor RS, Fritzell P, Taylor PJ. Balloon kyphoplasty in the management of vertebral compression fractures: an updated systematic review and meta-analysis. *Eur Spine J*. 2007;16(8): 1085–100.
43. Gu CN, Brinjikji W, Evans AJ, Murad MH, Kallmes DF. Outcomes of vertebroplasty compared with kyphoplasty: a systematic review and meta-analysis. *J Neurointerv Surg*. 2016;8(6):636–42.
44. Wang H, Sribastav SS, Ye F, et al. Comparison of percutaneous vertebroplasty and balloon kyphoplasty for the treatment of single level vertebral compression fractures: a meta-analysis of the literature. *Pain Physician*. 2015;18(3):209–22.
45. Pfeifer M, Begerow B, Minne HW. Effects of a new spinal orthosis on posture, trunk strength, and quality of life in women with postmenopausal osteoporosis: a randomized trial. *Am J Phys Med Rehabil*. 2004;83(3):177–86.
46. Pfeifer M, Kohlwey L, Begerow B, Minne HW. Effects of two newly developed spinal orthoses on trunk muscle strength, posture, and quality-of-life in women with postmenopausal osteoporosis: a randomized trial. *Am J Phys Med Rehabil*. 2011;90(10):805–15.
47. Kim HJ, Yi JM, Cho HG, et al. Comparative study of the treatment outcomes of osteoporotic compression fractures without neurologic injury using a rigid brace, a soft brace, and no brace: a prospective randomized controlled non-inferiority trial. *J Bone Joint Surg Am*. 2014;96(23):1959–66.
48. Li M, Law SW, Cheng J, Kee HM, Wong MS. A comparison study on the efficacy of SpinoMed(R) and soft lumbar orthosis for osteoporotic vertebral fracture. *Prosthet Orthot Int*. 2015;39(4):270–6.
49. Yang L, He CQ, Lei ZJ, et al. Effect of pain-free exercises on female osteoporosis patients with spinal fracture. *J Clin Rehabil Tissue Eng Res*. 2007;11(45):9108–11.
50. Bennell KL, Matthews B, Greig A, et al. Effects of an exercise and manual therapy program on physical impairments, function and quality-of-life in people with osteoporotic vertebral fracture: a randomised, single-blind controlled pilot trial. *BMC Musculoskelet Disord*. 2010;11:36.
51. Wang XF, Xu B, Ue XY, Yang YY, Wang GH. Effects of different treatments on patients with osteoporotic fracture after percutaneous kyphoplasty. *Zhongguo Gu Shang*. 2015;28(6):512–6.
52. Malmros B, Mortensen L, Jensen MB, Charles P. Positive effects of physiotherapy on chronic pain and performance in osteoporosis. *Osteoporos Int*. 1998;8(3):215–21.
53. Gold DT, Shipp KM, Peiper CF, et al. Group treatment improves trunk strength and psychological status in older women with vertebral fractures: results of a randomized, clinical trial. *J Am Geriatr Soc*. 2004;52(9):1471–8.
54. Bergland A, Thorsen H, Karesen R. Effect of exercise on mobility, balance, and health-related quality of life in osteoporotic women with a history of vertebral fracture: a randomized, controlled trial. *Osteoporos Int*. 2011;22(6):1863–71.
55. Papaioannou A, Adachi JD, Winegard K, et al. Efficacy of home-based exercise for improving quality of life among elderly women with symptomatic osteoporosis-related vertebral fractures. *Osteoporos Int*. 2003;14(8):677–82.
56. Evstigneeva L, Lesnyak O, Bultink IE, et al. Effect of twelve-month physical exercise program on patients with osteoporotic vertebral fractures: a randomized, controlled trial. *Osteoporos Int*. 2016;27(8): 2515–24.
57. Bergstrom I, Bergstrom K, Grahn Kronhed A-C, et al. Back extensor training increases muscle strength in postmenopausal women with osteoporosis, kyphosis and vertebral fractures. *Adv Physiother*. 2011;13(3):110–7.
58. Malmros B, et al. [Effect of specific physiotherapy on chronic pain, functional level and quality of life in osteoporosis. A prospective randomized single-blind placebo-controlled study]. *Ugeskr Laeger*. 1999;161(33):4636–41.
59. Shipp KM, et al. Improving trunk strength and endurance in older women with vertebral fractures. *J Bone Miner Res*. 2007;W398.
60. Olsen CF, Bergland A. The effect of exercise and education on fear of falling in elderly women with osteoporosis and a history of vertebral fracture: results of a randomized controlled trial. *Osteoporos Int*. 2014;25(8):2017–25.
61. Gibbs JC, et al. Exercise for improving outcomes after osteoporotic vertebral fracture: an update. *Cochrane Database Syst Rev*. 2016.